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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/000,439	10/24/2001	Andrew Saxon	UC067.004A	9201

25213 7590 06/20/2005

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/000,439	SAXON, ANDREW	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-6,9-14,16-34 and 40-49* is/are pending in the application.

4a) Of the above claim(s) *45-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-6, 9-14, 16-34 and 40-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 March 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/14/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 4-6, 9-14, 16-34 and 40-49 are pending.

2. Claims 45-49 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. The drawing filed 3/22/05 stands object to because the newly submitted Figure 9 is still completely dark. One cannot discern the content of the Figure.

4. The following new grounds of rejections are necessitated by the amendment filed 3/22/05.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 4-6, 9-14, 16-34 and 40-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an isolated fusion molecule comprising hinge-CH2-CH3 of human IgG1 constant region consisting of SEQ ID NO: 2 encoded by SEQ NO: 1 capable of binding to a native IgG inhibitory receptor directly fused to a full length myelin basic protein comprising SEQ ID NO: 12 or a myelin basic protein epitope consisting of SEQ ID NO: 13 wherein the fusion molecule is capable of specific binding to a native IgE receptor through a myelin protein specific IgE antibody, and (2) an isolated fusion molecule comprising hinge-CH2-CH3 of human IgG1 constant region consisting of SEQ ID NO: 1 fused to human IgE constant region CH2-CH3-CH4 domains for inhibiting IgE mediated release of histamine for treating allergy, **does not** reasonably provide enablement for any fusion molecule as set forth in claims 1, 4-6, 9-14, 16-34 and 40-44 comprising (1) first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor such as low-affinity FcγRIIb IgG receptor, directly functionally connected to (2) any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide sequence specific for myelin basic protein, to any native IgE

receptor, (3) the fusion molecule comprising any first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide sequence specific for myelin basic protein, to a native IgE receptor wherein said autoantigen sequence comprises at least one autoantigen, (4) the fusion molecule comprising any first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide sequence specific for myelin basic protein, to a native IgE receptor wherein said third polypeptide is any "immunoglobulin" capable of specific binding to a native IgE receptor, (5) the fusion molecule comprising any first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide sequence specific for myelin basic protein, to a native IgE receptor wherein said immunoglobulin is an IgE class antibody, (6) the fusion molecule comprising any first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide sequence specific for myelin basic protein, to a native IgE receptor wherein said autoantigen sequence present in said fusion molecule "comprises" at least any portion of the amino acid sequence of myelin basic protein, such as autoantigen "comprises" the amino acid sequence of SEQ ID NO: 13, (7) the fusion molecule comprising any first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific

binding, through any third polypeptide sequence specific for myelin basic protein, to a native IgE receptor wherein said IgE receptor is any high affinity FcεRI IgE receptor or any low-affinity FcεRII IgE receptor, (8) the fusion molecule comprising any first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide sequence specific for myelin basic protein, to a native IgE receptor wherein said autoantigen sequence comprises at least one autoantigen wherein said inhibitory receptor is FcγRIIb and FcεRI receptors are of human origin, (9) the fusion molecule comprising any first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide sequence specific for myelin basic protein, to a native IgE receptor wherein said autoantigen sequence comprises at least one autoantigen wherein said IgG is any IgG1, Igg2, IgG3 and IgG4, (10) the fusion molecule comprising any first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide sequence specific for myelin basic protein, to a native IgE receptor wherein said autoantigen sequence comprises at least one autoantigen wherein said IgG heavy chain constant region sequence is the native human IgG heavy chain constant region sequence of SEQ ID NO: 2, (11) the fusion molecule comprising any first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide sequence specific for myelin basic protein, to a native IgE receptor wherein said autoantigen sequence comprises at least one autoantigen wherein the first polypeptide sequence "comprises" any amino acid sequence such as having at least 85%, 90%, 95%, or 98% identity to the amino

acid sequence of SEQ ID NO: 3 or "comprises at least part of the CH2 and CH3 domains of a native human IgG1 constant region, or "comprises" at least part of the hinge of a native human IgG1 constant region or "comprises" at least part of the hinge, CH2 and CH3 domains of a native human IgG1 heavy chain constant region in the absence of a functional CH1 region, (12) the fusion molecule comprising any first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide sequence specific for myelin basic protein, to a native IgE receptor wherein said autoantigen sequence comprises at least one autoantigen wherein said first polypeptide sequence comprises any amino acid sequence encoded by any nucleic acid "hybridizing under stringent conditions" to at least any portion of the complement of the IgG heavy chain constant region nucleotide sequence of SEQ ID NO: 1, (13) the fusion molecule comprising any first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide sequence specific for myelin basic protein, to a native IgE receptor wherein said autoantigen sequence comprises at least one autoantigen wherein said first and second polypeptide are functional connected though a linker such as a linker consists of about 5 to about 25 amino acid residues, (14) the fusion molecule comprising any first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide sequence specific for myelin basic protein, to a native IgE receptor wherein said autoantigen sequence comprises at least one autoantigen wherein said fusion protein comprises at least one amino terminal ubiquitination target motif, or comprises at least one proteasome proteolysis signal such as large hydrophobic amino acid residues, basic amino acid residues and acid amino acid residues, (15) the fusion molecule comprising any first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor, directly

functionally connected to any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide sequence specific for myelin basic protein, to a native IgE receptor wherein said autoantigen sequence comprises at least one autoantigen wherein the polypeptide linker "comprises" at least one endopeptidase recognition motif or a plurality of endopeptidase recognition motifs wherein the endopeptidase recognition motif is selected from the group consisting of cysteine, aspartate and asparagines amino acid residues, (16) any pharmaceutical composition comprising any fusion molecule comprising any first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide sequence specific for myelin basic protein, to a native IgE receptor wherein said autoantigen sequence comprises at least one autoantigen mentioned above in admixture with a pharmaceutically acceptable excipient, and (17) any article of manufacture comprising a container, any fusion molecule comprising any first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide sequence specific for myelin basic protein, to a native IgE receptor wherein said autoantigen sequence comprises at least one autoantigen mentioned above within the container and a label or package insert on or associated with the container for treatment or "prevention" of any autoimmune disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient

to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only an isolated fusion molecule comprising a hinge-CH2-CH3 of human IgG1 constant region consisting of SEQ ID NO: 2 encoded by SEQ ID NO: 1 fused to a full length myelin basic protein comprising SEQ ID NO: 12 or a myelin basic protein epitope consisting of SEQ ID NO: 13, and (2) an isolated fusion molecule the hinge-CH2-CH3 of human IgG1 constant region consisting of SEQ ID NO: 1 fused to human IgE constant region CH2-CH3-CH4 domains of SEQID NO: 7 for inhibiting IgE mediated release of histamine.

The specification does not teach how to make and use all fusion molecule mentioned above for treating any autoimmune disease because the amino acid sequence of the fusion molecule is required. Further, there is insufficient guidance as to the structure of the first polypeptide "comprising at least 85% identity" with which IgG heavy chain constant region because the term "comprises" is open-ended. It expands the IgG heavy chain constant region to include the Fab region of the whole IgG. Without the amino acid sequence of the IgG heavy chain constant region or the whole IgG, one of skill in the art cannot make the fusion molecule. In addition to the problem mentioned above, the term "at least 85% identity" means there is at least 15% difference. Without knowing the length of the first polypeptide, it is not clear how one skill in the art to come up with the sequence identity that based on the total number of amino acids in the first polypeptide. Even if the length of the sequence is recited in the claim, there is insufficient guidance as to which amino acids within the IgG heavy chain constant region to be substituted, deleted, added and/or combination thereof such that the resulting IgG heavy chain constant region still binds to the native IgG inhibitory receptor.

With regard to the "second polypeptide" of the claimed isolated fusion molecule, the same reasons apply. There is insufficient guidance as to which "portion" of the amino acid sequence of myelin basic protein (MBP) is part of the fusion molecule without the amino acid sequence. Further, there is inadequate guidance as to which amino acids to be added, deleted, substituted and/or combination thereof such that the autoantigen comprising at least 10% difference still be able to bind to any native "IgE receptor" through any third polypeptide sequence, especially the third polypeptide is *any* immunoglobulin instead of IgE class antibody (claim 5). The specification and the art do not teach immunoglobulin such as IgG is capable of binding to IgE receptor. In fact, the specification discloses binding between second polypeptide and an IgE receptor occurs indirectly via specific IgE molecules (see page 36, lines 10), not any

immunoglobulin as recited in claim 5. Given the unlimited number of fusion molecule, there is a lack of in vivo working example demonstrating any fusion molecule is effective for treating autoimmune disease such as multiple sclerosis, let alone "preventing" any autoimmune disease as recited in claim 44.

Stryer *et al*, of record, teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al*, PTO 1449, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

McDevitt et al teach administering autoantigen such as epitopes 206-220, 221-235 and 286-300 of GAD to NOD mice suffer the prompt onset of an immediate hypersensitivity and death of animal (page 14628, col. 2, last paragraph, in particular). Without guidance as to the portion or epitope of autoantigen to be fused to the any IgG heavy chain constant region, it is unpredictable which fusion molecule is effective for treating any and all autoimmune disease.

With regard to percentage of sequence identity (claims 1 and 18-21), in addition to the lack sequence for the first, and second polypeptides in the fusion molecule mentioned above, there is insufficient guidance as to which amino acids within the full-length polypeptide can be modified and yet maintain its function. It is known in the art that the relationship between the amino acid sequence of a protein (polypeptide) and its tertiary structure (i.e. its binding activity) are not well understood and are not predictable (see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz, et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495). There is no recognition in the art that sequence with identity predicts biological function. It is known in the art that even a single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. Mikayama *et al.*, teach that the human glycosylation-inhibiting factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (Figure 1 in particular). Yet, Mikayama *et al.* further teach that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF bioactivity (Abstract in particular). It is also known in the art that amino acid sequence determines the function of the polypeptide or protein. However, the predictability of which changes can be tolerated in an amino acid sequence and still retain similar functions and

properties requires a knowledge of, and guidance such as which amino acids within the full-length polypeptide are tolerant of modification and which amino acid residues are conserved or less tolerant to modification in which the product's structure relates to its functional usefulness. The use of "percent" in conjunction with any of the various terms that refer to sequence identity or similarity is a problem because sequence identity between two sequences has no common meaning within the art. The term "percent" is relative and can be defined by the algorithm and parameter values set when using the algorithm used to compare the sequences. The scoring of gaps when comparing one sequence to another introduces uncertainty as to the percent of similarity between two sequences.

Because applicants have not disclosed the specific condition used to score sequence identity while using any computer program, it is unpredictable to determine which amino acid sequences of autoantigen in the claimed fusion molecule will have at least about 90% identity to which portion of myelin basic protein fused to which first polypeptide will have at least 85% sequence identity to which IgG heavy chain is effective for treating multiple sclerosis. Even if the autoantigen is "comprises at the amino acid sequence of SEQ ID NO: 13 (claim 10), SEQ ID NO: 13 is an epitope or fragment of myelin basic protein. The term "comprises" expands the fragment to include additional amino acids at either or both ends of SEQ ID NO: 3.

Warrant et al (abstract) teach administering myelin basic protein fragment such as MBP35-58 to multiple sclerosis patient had to effect on the anti-MBP level. However, only administering MBP 75-95 resulted in a significant in the autoantibodies over a period of one month (see abstract, in particular). The specification as filed does not teach which amino acids to be added and whether any fragment of myelin basic protein when fused to any first polypeptide comprising at least 85% identity is effective for treating autoimmune multiple sclerosis. Likewise, the same reasons apply to claims 18-21.

Attwood *et al.* teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable (See figure, entire document).

With regard to claims 24, the term "comprises" is open-ended. It extends the hinge, CH2 and CH3 domains of a native human IgG1 heavy chain constant region to include the light chain such as Fab fragment of the full-length human antibody.

With regard to the first polypeptide sequence comprises any amino acid sequence encoded by any nucleic acid hybridizing under stringent conditions to which "portion" of the complement of the IgG heavy chain constant region nucleotide of SEQ ID NO: 1 (claim 25), the nucleic acid that hybridizes to the complement of SEQ ID NO: 1 could be an oligonucleotide, which does not encodes the whole IgG heavy chain constant region, let alone binding to a native IgG inhibitory receptor. There is insufficient guidance as to the structure of the oligonucleotide that encodes which portion of the complement of IgG heavy chain constant region that binds native IgG native receptor in the claimed fusion molecule. Further, there is insufficient guidance as to the "hybridization conditions". The state of the prior art as exemplified by Wallace *et al,* of record, is such that determining the specificity of the oligo and hybridization conditions are empirical by nature and the effect of mismatches within an oligonucleotide probe is unpredictable. The claim as written is improper for an isolated fusion molecule.

Skolnick *et al*, PTO 1449, teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular). Given the unlimited number of undisclosed fusion molecules, there is insufficient in vivo working example demonstrating that any fusion molecules are effective for treating all autoimmune diseases. It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions could result in substantially different biological or pharmacological activities. Even if the fusion molecule is limited to human Fc fused to the myelin basic protein, there is a lack of in vivo working example demonstrating that the fusion is effective for treating multiple sclerosis. Without the structure, i.e., amino acid sequence of the fusion molecule, it is unpredictable which fusion molecule is effective for treating or preventing any autoimmune disease, any autoimmune disease such as multiple sclerosis.

With regard to pharmaceutical composition or article comprising any fusion molecule for treating any autoimmune disease, a pharmaceutical composition in the absence of in vivo is unpredictable for the following reasons: (1) the fusion molecule may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the fusion molecule may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the fusion molecule unsuitable for in vivo therapeutic use, i.e.

such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Blanas *et al* (of record, Science 274: 1707-1709, Dec 1996; PTO 1449) teach treating autoimmune rheumatoid arthritis and multiple sclerosis by oral administering autoantigen could lead to onset of autoimmune diabetes (see abstract, in particular).

Couzin *et al*, of record, teach that finding the telltale antibodies doesn't guarantee that autoimmune diabetes sill strike (See page 1863, Science 300: 1862-65, 2003). Couzin *et al* teach that three major prevention trials have failed to stop autoimmune disorder such as type I diabetes (See entire document).

Mackay *et al,* PTO 1449, teach that two recent phase I clinical trial for treatment of multiple sclerosis by administering myelin basic protein peptide resulted in exacerbations of multiple sclerosis (See page 346, col. 2, in particular). In the absence of guidance and vivo working example, it is unpredictable which undisclosed fusion molecule is useful for treating multiple sclerosis, let alone for "preventing" said autoimmune disease.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

7. Claims 1, 4-6, 9-14, 16-34 and 40-44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of any and any fusion molecule as set forth in claims 1, 4-6, 9-14, 16-34 and 40-44 comprising (1) first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor such as low-affinity FcγRIIb IgG

receptor, directly functionally connected to (2) any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide sequence specific for myelin basic protein, to any native IgE receptor, (3) the fusion molecule comprising any first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide sequence specific for myelin basic protein, to a native IgE receptor wherein said autoantigen sequence comprises at least one autoantigen, (4) the fusion molecule comprising any first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide sequence specific for myelin basic protein, to a native IgE receptor wherein said third polypeptide is any "immunoglobulin" capable of specific binding to a native IgE receptor, (5) the fusion molecule comprising any first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide sequence specific for myelin basic protein, to a native IgE receptor wherein said immunoglobulin is an IgE class antibody, (6) the fusion molecule comprising any first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide sequence specific for myelin basic protein, to a native IgE receptor wherein said autoantigen sequence present in said fusion molecule "comprises" at least any portion of the amino acid sequence of myelin basic protein, such as autoantigen "comprises" the amino acid sequence of SEQ ID NO: 13, (7) the fusion molecule comprising any first polypeptide sequence "comprising at least 85% identity" with any IgG heavy

chain constant region capable of binding to a native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide sequence specific for myelin basic protein, to a native IgE receptor wherein said IgE receptor is any high affinity FcεRI IgE receptor or any low-affinity FcεRII IgE receptor, (8) the fusion molecule comprising any first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide sequence specific for myelin basic protein, to a native IgE receptor wherein said autoantigen sequence comprises at least one autoantigen wherein said inhibitory receptor is FcγRIIb and FcεRI receptors are of human origin, (9) the fusion molecule comprising any first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide sequence specific for myelin basic protein, to a native IgE receptor wherein said autoantigen sequence comprises at least one autoantigen wherein said IgG is any IgG1,.Igg2, IgG3 and IgG4, (10) the fusion molecule comprising any first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide sequence specific for myelin basic protein, to a native IgE receptor wherein said autoantigen sequence comprises at least one autoantigen wherein said IgG heavy chain constant region sequence is the native human IgG heavy chain constant region sequence of SEQ ID NO: 2, (11) the fusion molecule comprising any first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide

sequence specific for myelin basic protein, to a native IgE receptor wherein said autoantigen sequence comprises at least one autoantigen wherein the first polypeptide sequence "comprises" any amino acid sequence such as having at least 85%, 90%, 95%, or 98% identity to the amino acid sequence of SEQ ID NO: 3 or "comprises at least part of the CH2 and CH3 domains of a native human IgG1 constant region, or "comprises" at least part of the hinge of a native human IgG1 constant region or "comprises" at least part of the hinge, CH2 and CH3 domains of a native human IgG1 heavy chain constant region in the absence of a functional CH1 region, (12) the fusion molecule comprising any first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide sequence specific for myelin basic protein, to a native IgE receptor wherein said autoantigen sequence comprises at least one autoantigen wherein said first polypeptide sequence comprises any amino acid sequence encoded by any nucleic acid "hybridizing under stringent conditions" to at least any portion of the complement of the IgG heavy chain constant region nucleotide sequence of SEQ ID NO: 1, (13) the fusion molecule comprising any first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide sequence specific for myelin basic protein, to a native IgE receptor wherein said autoantigen sequence comprises at least one autoantigen wherein said first and second polypeptide are functional connected though a linker such as a linker consists of about 5 to about 25 amino acid residues, (14) the fusion molecule comprising any first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide sequence specific for myelin basic protein, to a native IgE receptor wherein said autoantigen sequence comprises at least one autoantigen wherein said fusion protein comprises at least one amino terminal ubiquitination target motif, or comprises at least one proteasome proteolysis signal such as large hydrophobic

amino acid residues, basic amino acid residues and acid amino acid residues, (15) the fusion molecule comprising any first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide sequence specific for myelin basic protein, to a native IgE receptor wherein said autoantigen sequence comprises at least one autoantigen wherein the polypeptide linker "comprises" at least one endopeptidase recognition motif or a plurality of endopeptidase recognition motifs wherein the endopeptidase recognition motif is selected from the group consisting of cysteine, aspartate and asparagines amino acid residues, (16) any pharmaceutical composition comprising any fusion molecule comprising any first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide sequence specific for myelin basic protein, to a native IgE receptor wherein said autoantigen sequence comprises at least one autoantigen mentioned above in admixture with a pharmaceutically acceptable excipient, and (17) any article of manufacture comprising a container, any fusion molecule comprising any first polypeptide sequence "comprising at least 85% identity" with any IgG heavy chain constant region capable of binding to a native IgG inhibitory receptor, directly functionally connected to any second polypeptide autoantigen comprising "at least 90% sequence identity to at least *any* portion of the amino acid sequence of myelin basic protein (MBP)" and capable of specific binding, through any third polypeptide sequence specific for myelin basic protein, to a native IgE receptor wherein said autoantigen sequence comprises at least one autoantigen mentioned above within the container and a label or package insert on or associated with the container for treatment or "prevention" of any autoimmune disease.

The specification discloses only an isolated fusion molecule comprising a hinge-CH2-CH3 of human IgG1 constant region consisting of SEQ ID NO: 2 encoded by SEQ ID NO: 1 fused to a full length myelin basic protein comprising SEQ ID NO: 12 or a myelin basic protein epitope consisting of SEQ ID NO: 13, and (2) an isolated fusion molecule the hinge-CH2-CH3 of human IgG1 constant region consisting of SEQ ID NO: 1 fused to human IgE constant region

CH2-CH3-CH4 domains of SEQID NO: 7 for inhibiting IgE mediated release of histamine for treating allergy.

With the exception of the specific fusion molecule mentioned above, there is insufficient written description about the structure associated with function of any and all fusion molecules mentioned above because the amino acid sequence of the fusion molecule is required. With the amino acid sequence, there is no structure. Further, there is inadequate written description about the structure of the first polypeptide "comprising at least 85% identity" with which IgG heavy chain constant region because the term "comprises" is open-ended. It expands the IgG heavy chain constant region to include the Fab region of the whole IgG. In addition, the term "at least 85% identity" means there is at least 15% difference. Not only the length of the first polypeptide is not adequately described, there is inadequate written description about which amino acids within the undisclosed constant region of IgG to be substituted, deleted, added and/or combination thereof such that the first polypeptide still binds to the native IgG inhibitory receptor in the fusion molecule. The same reasoning apply to the first polypeptide as set forth in claim 18-21. Likewise, term "comprises" in claims 22-24 expands the first polypeptide sequence (immunoglobulin Fc region) in the fusion molecule to include additional amino acids at either or both ends in addition to part of the CH2, CH3 and hinge region to include CH1, CH4 and Fab fragment.

With regard to the second polypeptide of the claimed isolated fusion molecule, the same reasons apply. There is insufficient guidance as to which "portion" of the amino acid sequence of myelin basic protein (MBP) is part of the fusion molecule without the amino acid sequence. Further, there is inadequate disclosure about which amino acids within the portion to be added, deleted, substituted and combination thereof such that the autoantigen comprising at least 10% difference still be able to bind to any native "IgE receptor" through any third polypeptide sequence, especially the third polypeptide is any immunoglobulin instead of IgE class antibody (claim 5).

With regard to claim 9, there is inadequate written description about the "portion" of myelin basic protein without the amino acid sequence. Further, the term "comprises" is open-ended. It expands the undisclosed "portion" of the myelin basic protein to include additional amino acids at either or both ends. There is insufficient disclosure about which amino acids to be added, much less for the function of the said fragment.

Even the autoantigen sequence in the fusion protein comprises the amino acid sequence of SEQ ID NO: 13 (claim 10), SEQ ID NO: 13 is a fragment or epitope of myelin basic protein. Again, the term "comprises" is open-ended. It expands SEQ ID NO: 13 to include additional amino acids at either or both ends. There is insufficient disclosure about which amino acids to be added, much less for the function of the said fragment.

With regard to claim 25, in addition to the problem of "comprises", there is also inadequate written description about the nucleic acid sequence that "hybridizes" to which portion of the complement of the IgG heavy chain constant region of SEQ ID NO: 1, much less about the "stringent hybridization conditions" in the claimed fusion molecule given that the hybridization condition is sequence dependent. The nucleic acid that hybridizes to the complement of SEQ ID NO: 1 could be an oligonucleotide, which does not encodes the whole IgG heavy chain constant region, let alone binding to a native IgG inhibitory receptor. The structure of the oligonucleotide that encodes which portion of the complement of IgG heavy chain constant region that binds native IgG native receptor in the claimed fusion molecule is not adequately described. Further, claim 25 as written is improper for an isolated fusion molecule.

Adequate written description requires more than a mere statement that it is part of the invention. The amino acid sequence itself for the fusion molecule is required. Until the amino acid sequences of the first, and second polypeptides in the fusion protein have been described, the fusion molecule comprising the first and second polypeptide is not adequately described. Since the fusion molecule is not adequately described, it follows that the pharmaceutical composition and article of manufacture comprising said fusion molecules are not adequately described.

Finally, the specification discloses only three fusion molecules wherein the fusion molecule comprises a hinge-CH2-CH3 from only human IgG1 constant region consisting of SEQ ID NO: 2 fused to only myelin basic protein comprising SEQ ID NO: 12 (full length) or a peptide from myelin basic protein consisting of SEQ ID NO: 13, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of fusion molecule to describe the genus of fusion molecule for the claimed method. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claim 1, 4-6, 9-14, 16, 22-28, and 40-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,420,247 (May 30, 1995; PTO 892) in view of Warren *et al* (Proc Natl Acad Sci USA 92: 11061-65, November 1995; PTO 892) and Tisch et al (J Immunology 166: 2122-2132, Feb 2001; PTO 892).

The '247 patent teaches an isolated fusion molecule comprising a first polypeptide such as human IgG Fc constant region functionally connected to a second autoantigen polypeptide sequence such as human LIFR that is capable specific binding to LIF ligand through a third polypeptide sequence such as a polypeptide linker (See Figure 3, col. 12, line 36, col. 14, lines 43-52, col. 13, line 55-63, claim 4 of '247 patent, in particular). The reference native human Fc constant region from IgG1 comprises at least part of the hinge region and obviously is capable of binding to a native IgG inhibitory receptor such as low affinity FcγRIIb IgG receptor that comprises the an immune receptor-based inhibitory motif (ITIM) (See col.14, line 26-66, in particular). Because the reference first polypeptide is the same as the claimed first polypeptide in the claimed fusion molecule, the amino acid sequence encoded by a nucleic acid would hybridize under stringent conditions to at least a portion of the complement of the IgG heavy chain constant region nucleotide sequence of claimed SEQ ID NO: 1. The reference polypeptide linker such as (Gly4Ser)n where n is 4, which is within the claimed range of about 5 to about 25 amino acid residues. The reference linker sequence comprises asparagine amino acid residues and inherently

these asparagines are also an endopeptidase recognition motif (see col. 13, line 57-63, in particular). The '247 patent further teaches a pharmaceutical composition comprising the reference fusion molecule in admixture with a pharmaceutically acceptable excipient such as sucrose (See col. 21 lines 66 bridging col. 22, lines 1-30, in particular). The '247 patent teaches that IgG Fc fusion molecule can easily be purified using protein A or protein G affinity chromatography (See col. 33, lines 35-47, in particular). Claims 22-24 are included in this rejection because the term "comprises" is open-ended. It expands the IgG to include additional amino acid to include the hinge, CH2, CH3 domains. Claim 25 is included in this rejection because the recitation of nucleic acid hybridizing under stringent conditions to at least a portion of the complement of the IgG heavy chain constant region of claimed human IgG Fc of SEQ ID NO: 1 would obviously include the reference human IgG Fc.

The claimed invention as recited in claim 1 differs from the combined teachings of the references only in that the fusion molecule wherein the autoantigen sequence is at least 90% identity to at least a portion of the amino acid sequence of myelin basic protein (MBP).

Warren *et al* teach autoantigen sequence such as the full-length myelin basic protein (see Figure 3, page 11063, in particular) and various antigenic epitopes or fragment thereof such as MBP 84-93, and MBP89-95 (see page 11062, col. 2, in particular). The reference autoantigen is found in multiple sclerosis (see title, page 11065, in particular). The term "comprises" is open-ended. It expands the portion of myelin basic protein to include the reference full length MBP. The term "at least" includes the reference full length myelin basic protein that obviously comprises an amino acid sequence that is 100% identical E_{83}NPVVHFFKNIVTPRTP$_{99}$ of claimed SEQ ID NO: 13.

Tisch et al teach autoantigen such as GAD65 fused to the hinge, CH2 and CH3 of human IgG4 for treating autoimmune insulin-dependent diabetes mellitus (see page 2123, Materials and Methods, GAD65-IgFFc, in particular). Tisch et al teach the GAD65-specific sequence when fused to human IgG4Fc is secreted and the autoantigen specific epitope should be preferentially processed and presented via the MHC class II pathway (see page 2125, col. 1, results, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to substitute the LIF-R in the fusion molecule as taught by the '247 patent for autoantigen such as myelin basic protein (MBP) as taught by Warren *et al* for a fusion molecule comprising a first polypeptide IgG heavy chain constant region that capable of binding to IgG

inhibitory receptor such as the low affinity FcγRIIb directly functionally connected to myelin basic protein through a polypeptide linker as taught by the '247 patent and Warren *et al.* Alternatively it would be been obvious to one having ordinary skill in the art at the time the invention was made to substitute the autoantigen GA65 in the fusion molecule as taught by Tisch et al for the myelin basic protein as taught by Warren *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '247 patent teaches that IgG Fc fusion molecule can easily be purified using protein A or protein G affinity chromatography (See col. 33, lines 35-47, in particular). Tisch et al teach the autoantigen-specific sequence when to human IgG Fc is secreted and the autoantigen specific epitope should be preferentially processed and presented via the MHC class II pathway and is useful for treating autoimmune disease (see page 2125, col. 1, results, in particular). Claim 6 is included in this rejection because the reference fusion molecule comprising Fc fused to myeline basic protein obviously recognizes by myelin basic protein specific IgE antibody and thereby capable of binding through a native IgE receptor. Claims 12-13 are included in this rejection because myelin basic protein fusion molecule obvious capable of binding to IgE receptor indirectly through myelin basic protein specific IgE antibody. Claim 14 is included in this rejection because the reference fusion molecule comprising human IgG1 Fc obviously binds to human FcγRIIb. Claims 22-24 are included in this rejection because the term "comprises" is open-ended. It extends the claimed at least part of the CH2 and CH3 domains of native human IgG1 constant region to the complete IgG Fc region as taught by the '247 patent.

Applicants' arguments filed 3/22/05 have been fully considered but are not found persuasive.

Applicants' position is that the '247 patent does not teach or suggest a fusion molecule of the IgG heavy chain constant region fused to MBP peptide. Warren does not teach or suggest fusion molecules of the MBP peptide with the IgG heavy chain constant region. There is no teaching or suggestion in the combination of the references to fuse the heavy constant region of the IgG molecule with a myelin basic peptide fragment.

In response, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller , 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc. , 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See

MPEP 2145. In response to applicant's argument that there is no teaching or suggestion in the combination of the references to fuse the heavy constant region of the IgG molecule with a myelin basic peptide fragment, Tisch et al teach the autoantigen-specific sequence when to human IgG4Fc is secreted and the autoantigen specific epitope should be preferentially processed and presented via the MHC class II pathway (see page 2125, col. 1, results, in particular). Warren *et al* teach autoantigen sequence such as the full-length myelin basic protein (see Figure 3, page 11063, in particular) and various antigenic epitopes or fragment thereof such as MBP 84-93, and MBP89-95 (see page 11062, col. 2, in particular).

11. Claims 1 and 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,420,247 (of record, May 30, 1995; PTO 892) in view of Warren *et al* (of record, Proc Natl Acad Sci USA 92: 11061-65, November 1995; PTO 892) and Tisch et al (J immunology 166: 2122-2132, February 2001; PTO 892) as applied to claims 1, 4-5, 9-14, 15-16, 22-28, and 40-41 mentioned above and further in view of US Pat No 5,565,335 (of record, Oct 1996; PTO 892).

The combined teachings of the '247 patent, Warren *et al* and Tisch et al have been discussed supra. .

The claimed invention in claim 18 differs from the combined teachings of the references only in that the fusion molecule wherein the first polypeptide sequence comprises an amino acid sequence having at least 85% identity to amino acid sequence of SEQ ID NO: 3.

The claimed invention in claim 19 differs from the combined teachings of the references only in that the fusion molecule wherein the first polypeptide sequence comprises an amino acid sequence having at least 90% identity to amino acid sequence of SEQ ID NO: 3.

The claimed invention in claim 20 differs from the combined teachings of the references only in that the fusion molecule wherein the first polypeptide sequence comprises an amino acid sequence having at least 95% identity to amino acid sequence of SEQ ID NO: 3.

The '335 patent teach various fusion molecule comprising IgG heavy chain constant region polypeptide having an amino acid sequence at least 97.2% identity to the claimed SEQ ID NO: 3, which is at least 85%, 90%, and 95% identical to the claimed SEQ ID NO: 3 (See reference SEQ ID NO 7, in particular) fused to a second polypeptide such as autoantigen CD4, myelin associated glycoprotein (See col. 4, Detailed description, lines 18-31, in particular). The reference Fc fusion molecule enhances the plasma half-life of the fusion molecule (see Summary of invention, col. 5, lines 26-47, Table IV, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to substitute the Fc polypeptide in the fusion molecule as taught by the '247 patent or the Fc IgG4 in the fusion molecule as taught by Tisch et al for the human IgG1 Fc having an amino acid sequence at least 97.2% identical to the claimed SEQ ID NO: 3 as taught by the '335 patent for a fusion molecule comprising a human IgG Fc constant region functionally connected to any second autoantigen polypeptide sequence such as MBP as taught by Warren *et al,* the '247 patent, Tisch et al and the '335 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '247 patent teaches that IgG Fc fusion molecule can easily be purified using protein A or protein G affinity chromatography (See col. 33, lines 35-47, in particular). Tisch et al teach the autoantigen-specific sequence when to human IgG4Fc is secreted and the autoantigen specific epitope should be preferentially processed and presented via the MHC class II pathway (see page 2125, col. 1, results, in particular). The '335 patent teaches that Fc fusion molecule enhances the plasma half-life of the fusion molecule and is useful for (see Summary of invention, col. 5, lines 26-47, in particular).

Applicants' arguments filed 3/22/05 have been fully considered but are not found persuasive.

Applicants' position is that there is no teaching or suggestion in the combination of the references to fuse the heavy constant region of the IgE molecule with a myelin basic peptide fragment. While the '247 patent teaches LIF-R fused with IgG, the purpose of adding IgG was to generate a dimer molecule. While the '335 patent teaches CD4 fused with IgG there is no teaching or suggestion to combine an MBP peptide with an IgG Fc region. Secondly, there is no motivation in the cited references to combine the teachings of the references to arrive at the claimed invention. The '247 patent uses the IgG heavy chain region to generate a dimer molecule to obtain the biologic function of the LIF molecule. It provides no motivation to replace the LIF-RM peptide with an MBP peptide. The '335 patent teaches CD4 fused with IgG. There is no motivation in the '335 patent to replace the CD4 with an MBP peptide. Finally, none of the references, either alone or in combination provide a reasonable expectation of success from the claimed invention.

In contrast to applicant's assertion that there is no motivation to replace or combine the teachings of the references to arrive at the claimed invention, Tisch et al teach the autoantigen-specific sequence when to human IgG4Fc is secreted and the autoantigen specific epitope should be preferentially processed and presented via the MHC class II pathway (see page 2125, col. 1, results, in particular). It would be been obvious to one having ordinary skill in the art at the time the invention was made to substitute the LIF-R in the fusion molecule as taught by the '247 patent for autoantigen such as myelin basic protein (MBP) as taught by Warren *et al* for a fusion molecule comprising a first polypeptide IgG heavy chain constant region that capable of binding to IgG inhibitory receptor such as low affinity FcγRIIb directly functionally connected to myelin basic protein as taught by the '247 patent and Warren *et al.* Alternatively it would be been obvious to one having ordinary skill in the art at the time the invention was made to substitute the autoantigen GA65 in the fusion molecule as taught by Tisch et al for the myelin basic protein as taught by Warren *et al.* The motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose. Section MPEP 2144.07. One having ordinary skill in the art at the time the invention was made would have been motivated with an expectation of success to do this because Tisch et al teach the autoantigen-specific sequence when to human IgG4Fc is secreted and the autoantigen specific epitope should be preferentially processed and presented via the MHC class II pathway which is useful for treating autoimmune disease (see page 2125, col. 1, results, in particular).

12. Claims 1, 27, and 29-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,420,247 (May 30, 1995; PTO 892) in view of Warren *et al* (of record, Proc Natl Acad Sci USA 92: 11061-65, November 1995; PTO 892) and Tisch et al (J immunology 166: 2122-2132, February 2001; PTO 892) as applied to claims 1, 4-5, 9-14, 15-16, 22-28, and 40-41 mentioned above and further in view of Elias et al (of record, J Biol Chem 265(26): 15511-17, September 1990; PTO 892) and Marks et al (of record, J Cell Biol 135(2): 341-354, Oct 1996; PTO 892).

The combined teachings of the '247 patent, Warren *et al* and Tisch et al have been discussed supra.

The claimed invention in claim 29 differs from the combined teachings of the references only in that the fusion molecule comprises at least one amino terminal ubiquitination target motif.

The claimed invention in claim 30 differs from the combined teachings of the references only in that the fusion molecule comprises at least one proteasome proteolytic signal, wherein said signal is selected from the group consisting of large hydrophobic amino acid residues, basic amino acid residues, and acidic amino acid residues.

The claimed invention in claim 31 differs from the combined teachings of the references only in that the fusion molecule comprises large hydrophobic amino acid residues, basic residues, and acid amino acid residues.

Elias et al teach N terminal residue of the protein is one important structural determinant recognized by ubiquitin ligase and conjugated protein to ubiquitin targets the protein for protein degradation (See page col. 15511, col. 2, second paragraph, in particular). Elias et al teach protein with hybrophobic amino acid residues such as leucine, or basic amino acid residues such as histidine, arginine and lysine determines the half-life of the protein (See paragraph, bridging page 15511 and 15512, in particular).

Marks et al teach that that adding ubiquitination target motif such as bulky hydrophobic group di-leucine motif to any protein would target the protein to the lysosome or endosomal compartments that is recognizes by the endopeptidase motif such as cysteine for antigen processing (See abstract, page 348, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to add at least one amino terminal ubiquitination target motif such as large hydrophobic amino acid residue such as leucine as taught by Elias and Marks to the fusion molecule as taught by the '247 patent or Tisch et al to target the transmembrane protein such as Ig Fc connected to myelin basic protein as taught by Warren *et al* through a peptide linker to route the fusion molecule to the lysosome and endosome antigen processing as well as modulating the half-life of the fusion molecule as taught by the Elias et al and Marks et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Elias et al teach adding hybrophobic amino acid residues such as leucine, or basic amino acid residues such as histidine, arginine and lysine to the amino terminal of any protein modulates the half-life of the protein (See page 1552, col. 1, in particular). Marks et al teach that that adding ubiquitination target motif such as bulky hydrophobic group di-leucine

motif to any protein would target the protein to the lysosome or endosomal compartments for antigen processing to be release from the cell (See abstract, page 348, in particular).

Applicants' arguments filed 3/22/05 have been fully considered but are not found persuasive.

Applicants' position is that claim 1 has been amended. First, there is no teaching or suggestion in the combination of the references to fuse the heavy constant region of the IgG molecule with a myelin basic peptide fragment. The '247 patent does not teach or suggest the fusion of a heavy constant region of the IgG molecule with a myelin basic peptide fragment. The Elias and Marks references do not cure this deficiency. Secondly, there is no motivation in the cited references to combine the teachings of the references to arrive at the claimed invention. The '247 patent uses the IgG heavy chain region to generate a dimer molecule. It provides no motivation to replace the LIF-Fc peptide with an MBP peptide. The Elias and Marks references do not cure this deficiency. Finally, none of the references, either alone or in combination provide a reasonable expectation of success from the claimed invention. Absent a suggestion in the ad to make the claimed invention, a motivation in the cited references to combine the references into the claimed invention and a reasonable expectation of success, the claimed invention is not obvious.

In contrast to applicant's assertion that there is no motivation to replace to combine the teachings of the references to arrive at the claimed invention, Tisch et al teach the autoantigen-specific sequence when to human IgG4Fc is secreted and the autoantigen specific epitope should be preferentially processed and presented via the MHC class II pathway (see page 2125, col. 1, results, in particular). It would be been obvious to one having ordinary skill in the art at the time the invention was made to substitute the LIF-R in the fusion molecule as taught by the '247 patent for autoantigen such as myelin basic protein (MBP) as taught by Warren *et al* for a fusion molecule comprising a first polypeptide IgG heavy chain constant region that capable of binding to IgG inhibitory receptor such as low affinity FcγRIIb directly functionally connected to myelin basic protein as taught by the '247 patent and Warren *et al.* Alternatively it would be been obvious to one having ordinary skill in the art at the time the invention was made to substitute the autoantigen GA65 in the fusion molecule as taught by Tisch et al for the myelin basic protein as taught by Warren *et al.* The motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose. Section MPEP 2144.07. One having ordinary skill in the art at

the time the invention was made would have been motivated with an expectation of success to do this because Tisch et al teach the autoantigen-specific sequence when to human IgG4Fc is secreted and the autoantigen specific epitope should be preferentially processed and presented via the MHC class II pathway which is useful for treating autoimmune disease (see page 2125, col. 1, results, in particular).

13. Claims 1, 9 and 42-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,420,247 (May 30, 1995; PTO 892) in view of Warren *et al* (of record, Proc Natl Acad Sci USA 92: 11061-65, November 1995; PTO 892) and Tisch et al (J immunology 166: 2122-2132, February 2001; PTO 892) as applied to claims 1, 4-5, 9-14, 15-16, 22-28, and 40-41 mentioned above and further in view of US Pat No 5,945,294 (of record, Aug 1999, PTO 892).

The combined teachings of the '247 patent, Warren *et al* and Tisch et al have been discussed supra.

The claimed invention in claims 42-44 differs from the combined teachings of the references only in that an article of manufacture comprising a container, a fusion molecule within the container, and a label or package insert on or associated with the container.

The '294 patent teaches diagnostic kit (for IgE detection using human Fc epsilon receptor (See abstract, in particular). The kit is useful for diagnosing abnormal conditions in animals that are associated with changing levels of IgE associated with allergy (See column 15, lines 19-23, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the human Fc epsilon receptor in a kit as taught by the '294 patent for the fusion protein as taught by the '247 patent, Warren et al and Tisch et al. One would have been motivated, with a reasonable expectation of success to do this for convenience and commercial expedience. A kit will allow for ease of use for the practitioner since all the necessary reagents, standard and instructions for use are included in a kit as taught by '294 (See column 14, in particular). From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Claim 44 is included in this rejection because a product is a product, irrespective of its intended use.

Applicants' arguments filed 3/22/05 have been fully considered but are not found persuasive.

Applicants' position is that the '247 patent has been discussed. The '294 patent teaches diagnostic kits for IgE detection comprising human Fc epsilon receptor and an allergen. Neither the '247 nor the '294 patent nor a combination of both teaches or suggests the fusion protein of the IgG Fc region with the MBP peptide in a kit. Absent such a teaching or suggestion, the invention is not obvious.

In contrast to applicant's assertion that the '247 nor the '294 patent nor a combination of both teaches or suggests the fusion protein of the IgG Fc region with the MBP peptide in a kit, the combined teachings of the '247 patent, Warren *et al* and Tisch et al have been discussed supra. The '294 patent teaches diagnostic kit (for IgE detection using human Fc epsilon receptor (See abstract, in particular). The kit is useful for diagnosing abnormal conditions in animals that are associated with changing levels of IgE associated with allergy (See column 15, lines 19-23, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the human Fc epsilon receptor in a kit as taught by the '294 patent for the fusion protein as taught by the '247 patent, Warren et al and Tisch et al. One would have been motivated, with a reasonable expectation of success to do this for convenience and commercial expedience. A kit will allow for ease of use for the practitioner since all the necessary reagents, standard and instructions for use are included in a kit as taught by '294 (See column 14, in particular). From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

14. Claim 17 is free of prior art.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

17. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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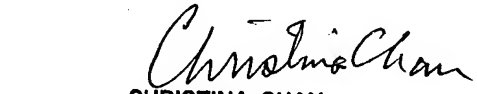
June 10, 2005



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